



US008153829B2

(12) **United States Patent**
Lemaire et al.

(10) **Patent No.:** US 8,153,829 B2
(45) **Date of Patent:** Apr. 10, 2012

(54) **METHODS FOR THE PREPARATION OF HEXAHYDROFURO[2,3-B]FURAN-3-OL**

(75) Inventors: Sébastien François Emmanuel Lemaire, Brussels (BE); Andras Horvath, Turnhout (BE); Wim Albert Alex Aelterman, Gierle (BE); Thomas Joachim Landewald Rammeloo, Vosselaar (BE)

(73) Assignee: Janssen Pharmaceutica N.V., Beerse (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 422 days.

(21) Appl. No.: 12/447,537

(22) PCT Filed: Nov. 9, 2007

(86) PCT No.: PCT/EP2007/062119

§ 371 (c)(1),

(2), (4) Date: Apr. 28, 2009

(87) PCT Pub. No.: WO2008/055970

PCT Pub. Date: May 15, 2008

(65) **Prior Publication Data**

US 2010/0094028 A1 Apr. 15, 2010

(30) **Foreign Application Priority Data**

Nov. 9, 2006 (EP) 06123752

(51) **Int. Cl.**

C07D 307/20 (2006.01)
C07D 493/04 (2006.01)

(52) **U.S. Cl.** 549/475; 549/464

(58) **Field of Classification Search** 549/464, 549/475

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,127,372 A	10/2000	Tung et al.
6,867,321 B2	3/2005	Ikemoto et al.
7,700,645 B2 *	4/2010	Vermeersch et al. 514/456
2004/0162340 A1	8/2004	Ikemoto et al.

FOREIGN PATENT DOCUMENTS

EP	0 715 618 A1	6/1996
EP	0 754 669 A1	1/1997
EP	1 029 856 A1	8/2000
EP	1 067 125 A1	1/2001
EP	1 081 133 A1	3/2001
EP	1 215 209 A1	6/2002
WO	WO 95/06030 A1	3/1995
WO	WO-95/24385 A1	9/1995
WO	WO-97/18205 A1	5/1997
WO	WO-99/65870 A2	12/1999
WO	WO-99/67254 A2	12/1999
WO	WO-99/67417 A2	12/1999
WO	WO-00/47551 A2	8/2000

WO	WO-00/76961 A1	12/2000
WO	WO-01/25240 A1	4/2001
WO	WO-02/060905 A2	8/2002
WO	WO 03/022853	3/2003
WO	WO-03/024974 A2	3/2003
WO	WO 2004/002975	1/2004
WO	WO-2004/033462 A2	4/2004
WO	WO-2005/063770 A1	7/2005
WO	WO-2005/095410 A1	10/2005

OTHER PUBLICATIONS

Ghosh, A.K. et al. "T1C14 Promoted Three Component Coupling Reaction: A New Method for the Synthesis of Functionalized Tetrahydrofurans and Tetrahydropyrans". *Tetrahedron Letters*, Elsevier, Amsterdam, NL., vol. 40, No. 6. Feb. 5, 1999, pp. 1083-1086, XP00415464.

Ghosh, A.K. et al. "Potent HIV Protease Inhibitors Incorporating High-Affinity P2-Ligands and (R)-(Hydroxyethylamino)Sulfonamide Isostere". *BioOrganic & Medicinal Chemistry Letters*, Oxford, GB, vol. 8, No. 6, Mar. 17, 1998, pp. 687-690, XP004136945.

Boyer et al., A New Method for the Reduction of Esters, *Synthesis*, 558-559, 1981.

Chuit et al., Improved Procedure for the Selective Reduction of Carbonyl Compounds and Carboxylic Acid Esters by Potassium Salt-Induced Hydrosilylation, *Synthesis*, 981-984, 1982.

Drew et al., A Convenient Procedure for the Reduction of Esters, Carboxylic Acids, Ketones and Aldehydes using Tetrabutylammonium Fluoride (or Triton® B) and Polymethylhydrosiloxane, *Synlett*, 989-997, 1997.

Ghosh et al., Nonpeptidal P₂ Ligands for HIV Protease Inhibitors: Structure-Based Design, Synthesis, and Biological Evaluation, *J. Med. Chem.*, 39(17):3278-3290, 1996.

Ghosh et al., Stereoselective Photochemical 1,3-Dioxolane Addition to 5-Alkoxymethyl-2(5H)-furanone: Synthesis of Bis-tetrahydrafuranyl Ligand for HIV Protease Inhibitor UIC-94017 (TMC-114), *J. Org. Chem.*, 69(23):7822-7829, 2004.

Ghosh et al., Synthesis and Optical Resolution of High Affinity P₂-Ligands for HIV-1 Protease Inhibitors, *Tetrahedron Letters*, 36(4):505-508, 1995.

Igarashi et al., Ruthenium Complex Catalyzed Hydrosilylation of Esters: a Facile Transformation of Esters to Alkyl Silyl Acetals and Aldehydes, *Tetrahedron Letters*, 42:2149-2151, 2001.

Marc, Reactions, Mechanisms, and Structure; *Advanced Organic Chemistry* 3rd Ed., 368-369, 1985.

McManus et al., The Synthesis of Aminoalcohols from Epoxides and Ammonia, *Synthetic Communications*, 3(3):177-180, 1973.

Mikami et al., Catalytic Asymmetric Glyoxylate-Ene Reaction: A Practical Access to α -Hydroxy Esters in High Enantiomeric Purities, *J. Am. Chem. Soc.*, 112(10):3949-3954, 1990.

Mimoun, Selective Reduction of Carbonyl Compounds by Polymethylhydrosiloxane in the Presence of Metal Hydride Catalysts, *J. Org. Chem.*, 64(7):2582-2589, 1999.

(Continued)

Primary Examiner — Bernard Dentz

(74) *Attorney, Agent, or Firm* — Woodcock Washburn LLP

(57) **ABSTRACT**

Methods for the preparation of hexahydrofuro[2,3-b]furan-3-ol and especially its enantiomer (3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-ol, as well as certain novel intermediates for use in such methods are disclosed.

20 Claims, No Drawings